REMARKS

Applicants' representative would like to thank Examiner Marx for the courteous and helpful interview of this application on November 4, 2003. During the interview the rejections of the claims under 35 USC 112, second paragraph and 35 USC 103(a) were discussed. The amendments to the claims reflect the amendments discussed in the interview.

In the Office Action of July 10, 2003, claims 1, 3-4, 6-8 and 12-13 were rejected under 35 USC 112, second paragraph as indefinite.

Claim 1 has been amended as suggested by the Examiner to state that the enzymes are present in effective amounts. Claim 13 has been amended to delete "biological organisms" and insert "bacteria, yeast or plant cells". Withdrawal of this section 112, second paragraph rejection is requested.

At page 3 of the Office Action of July 10, 2003, claims 1, 3-4, 6-8 and 12-13 were rejected under 35 USC 103(a) as being unpatentable over Suemori et al. (1995) taken with Blakley et al., Suemori et al. (1996) and Hareland et al. for the reasons stated in the previous Office Action, and for the additional reasons stated in the Office Action of July 10, 2003. The basis for the rejection is that it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of Suemori et al. (1995) by using further enzymes from other microorganisms for the bioconversion of HPP into HPA and the enzymatic bioconversion of HPA into HMO, in the presence of an HPPD inhibitor for the expected benefits of maximizing the yield of this valuable compound useful in a variety of pharmaceutical and industrial applications.

Applicants again traverse this rejection. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the Applicant. The cited references, by themselves, must teach or suggest the claimed invention and provide the motivation to combine the references in the manner necessary to produce the claimed invention. It is impermissible to engage in

a hindsight reconstruction of the claimed invention, using the Applicant's disclosure as a template and selecting elements from references to fill the gaps.

The present rejection does not establish a *prima facie* case of obviousness.

Suemori *et al.* (1995) discloses studies on the degradation of tyrosine in *R. erythropolis* where the authors concluded that tyrosine was degraded through HPP and HPA to HMO. This publication discloses that HPA-hydroxylase catalyzes the reaction of HPA to HMO, but does not disclose any enzyme that catalyzes the conversion of HPP to HPA. Figure 1 of this publication shows L-phenylalanine and L-tyrosine degradative pathways in *R. erythropolis*. Three enzymes are identified in the L-tyrosine pathway, aromatic amino acid oxidase, p-hydroxyphenylacetic acid 1-hydroxylase and homogentisate 1,2-dioxygenase, and their location in the pathway is shown. None of these enzymes catalyze the conversion of HPP to HPA. No enzyme that catalyzes the conversion of HPP to HPA is shown in Figure 1 or anywhere else in the publication. Additionally, Suemori *et al.* makes no suggestion whatever about the possibility or desirability of substituting enzymes from other microorganisms for the ones in *R. erythropolis* to produce HMO.

Suemori *et al.* (1996), Hareland *et al.* and Blakley *et al.* do not supply what is missing from Suemori *et al.*

Suemori *et al.* (1996) discloses purification and characterization of a HPA hydroxylase from the bacterium *R. erythropolis*. This publication, like Suemori et al. (1995) also fails to disclose any enzyme responsible for the bioconversion of HPP to HPA. Moreover, there is no suggestion in Suemori *et al.* (1996) of combining enzymes from other organisms to produce HMO.

Hareland *et al.* discloses HPA-hydroxylase from *Pseudomonas acidovarans*, but does not make any suggestion whatever about the possibility or desirability of substituting enzymes from other microorganisms to produce HMO. In the previous Office Action, the Examiner pointed out that Hareland et al. discusses HPP-oxidase inhibitors at page 279, Figure 7 and that some activity remains in every instance, even though relatively high concentrations of inhibitor are used. In the Office Action of July 10, 2003, the Examiner further added that Applicants have presented only attorney arguments without appropriate evidence that the compounds in Hareland et al. are not

HPPD inhibitors as required by the claims, and stated that "inasmuch as all that is required is the presence of an HPPD inhibitor, it cannot reasonably be concluded that that at some concentration the compounds of Table 3 of Hareland et al. do not act to inhibit HPPD, particularly in the absence of objective evidence to the contrary. The Examiner further indicated that the Applicants' disclosure of herbicidal compounds as HPPD inhibitors is not limiting and does not mean that other compounds do not act in this capacity, at least to some extent.

Figure 7 of Hareland et al. shows a graph of competitive inhibition of HPA-hydroxylase by various concentrations of 4-hydroxy-3-methylphenylacetic acid. Table 3 of Hareland et al. shows activities of analogues of 4-HPA as substrates or inhibitors of HPA-hydroxylase. Table 3 is discussed at pages 278-279 of Hareland et al. in the section entitled "Substrate analogues and inhibitors of 4-HPA 1-hydroxylase".
Hareland et al. discloses HPA-hydroxylase inhibitors (page 278-279), not HPPD inhibitors as required by Applicants' claimed method. Inhibitors of HPA-hydroxylase would not have been taken into account by persons skilled in the art for a method conducted in the presence of an HPPD inhibitor.

The Examiner's rationale for possible activity of the HPA-hydroxylase inhibitors as HPPD inhibitors is speculative and is an improper basis for rejecting the claims. In rejecting claims, a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art. There is no disclosure or suggestion in Hareland et al. that the compounds tested to determine their ability to act as substrates or inhibitors of HPA-hydroxylase also act as HPPD inhibitors. Hareland et al. therefore does not reasonably suggest to one skilled in the art that such compounds act as HPPD inhibitors. The Examiner cannot speculate upon other, undisclosed activity the compounds disclosed in Hareland et al. might possibly have to support a rejection of the claims.

Blakley et al. discloses experiments on the catabolism of L-tyrosine by an *Arthrobacter* species. The publication discloses that the *Arthrobacter* species metabolizes L-tyrosine by a pathway involving 3,4-dihydroxyphenylacetate (homoprotocachuate) as a key intermediate. By contrast, as stated on page 1128 of Blakley et al., the major pathway for the catabolism of L-tyrosine in mammals and

probably microorganisms involves homogentisate as a key intermediate. The pathway disclosed in this publication produces a different compound, 3,4-dihydroxyphenylacetate. The claims of the present application are directed to methods of producing HMO. Blakley et al. discloses HPP-oxidase from the *Athrobacter* species used in their experiments, but there is no suggestion whatever about the possibility or desirability of substituting enzymes from other microorganisms to produce HMO.

The motivation for combining the cited references provided by the Examiner in the present rejection indicated that persons skilled the art would seek to combine the teachings of the cited references for the expected benefits of maximizing the yield of HMO which is useful in a variety of pharmaceutical and industrial applications.

The case *In re Sang-Su Lee,* 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002) explains the type of explanation and reasoning that is required to establish a *prima facie* case of obviousness and emphasizes that Examiners must clearly explain how and why the teachings of the cited references provide the motivation to combine the references in the manner necessary to support the obviousness rejection. The Federal Circuit has made it very clear that Examiners cannot rely on conclusory statements, such as those used in the present rejection to establish the motivation to combine references.

The combination of Suemori *et al.* (1995) with Suemori *et al.* (1996), Hareland *et al.* and Blakley *et al.* amounts to an impermissible hindsight reconstruction of the claimed invention from isolated disclosures in the prior art. Three of the cited references disclose one of the enzymes used in the claimed methods, HPA-hydroxylase, but do not disclose the other enzyme used in the claimed methods, HPP-oxidase. Suemori et al. (1995), Suemori et al. (1996) and Hareland et al. disclose HPA-hydroxylase but not HPP-oxidase. None of these references disclose or suggest combining HPA-hydroxylase with any other enzyme, much less combining it with HPP-oxidase from other organisms to produce HMO. Blakley et al. discloses HPP-oxidase, but this publication discloses a different pathway than Suemori et al. (1995) for catabolism of L-tryosine. Persons skilled in the art would not be motivated to look to this publication for an element of the claimed invention because it does not deal with the preparation of HMO.

The cited references are isolated disclosures of enzymes that can be used in the claimed methods, but the references lack any motivation for one skilled in the art to

combine their disclosures to produce HMO as claimed by Applicants. Moreover, even if the cited combination of references were proper, the combined disclosures of the cited references still fails to disclose carrying out the enzymatic reactions in the presence of an HPPD inhibitor in the suitable reaction medium as required by the claims.

Applicants submit that the Examiner has not established a *prima facie* case of obviousness. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. The cited combination of references fails to disclose or suggest carrying out the enzymatic reactions in the presence of an HPPD inhibitor in the suitable reaction medium as required by the claims. Additionally, there is no motivation in the cited references, alone or in combination, that would lead a person skilled in the art to combine the disclosures to produce HMO as claimed by Applicants.

Applicants claimed methods for producing HMO are not obvious over the combination of Suemori *et al.* (1995) with Suemori *et al.* (1996), Hareland *et al.* and Blakley *et al.* Withdrawal of this section 103 rejection is respectfully requested.

In view of the above, the present application is believed to be in a condition for allowance. Reconsideration of the application is requested and an early Notice of Allowance is earnestly solicited.

Respectfully submitted,
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